collision.

DR. ROBINSON: Okay.

MR. YANG: The air bag situation we model as impact testing, not as fatigue testing.

DR. ROBINSON: I have one more for Dr. Cunningham.

CHAIRMAN WHALEN: Please.

DR. ROBINSON: Dr. Cunningham, towards the end of your presentation you had a group of patients that were explanted and then reimplanted. I think there was 60 of them if I remember correctly. I may be a little bit off on that. I may have missed it.

Is it too early to comment on those 60 that have been reimplanted?

DR. CUNNINGHAM: You're referring to the revision group?

DR. ROBINSON: I believe so. It was towards the end of your presentation, yeah.

DR. CUNNINGHAM: We can discuss the revision group.

MR. PURKAIT: Before we start the revision group, one question to answer Ms. Dubler about that,

no, we have not had that incorporated in the patient level. We would be doing that, the information about Betadine use.

And to answer your, Doctor -- I can see your --

DR. ROBINSON: Robinson.

MR. PURKAIT: -- Robinson, about the safety margin, the question that you have on fatigue, I'd just like to conclude that by saying the model that you have shown here is fatigue testing only to show the safety margin in terms of the load factor that it can take over a time period.

The question that you have is data impact. We have tested against a model called 35 miles per hour collision. If somebody had the amount of impact energy, it would be on the chest, whether it would withstand the breast or not, and we found that our product, it takes about three times more than impact energy to cause rupture.

So I just want to clarify that.

DR. ROBINSON: That's what I was looking for. Thanks.

MR. PURKAIT: Thank you.

To answer the question on the other areas, I'd like to call Dr. Gene Poggio to show some of the information, and then I'll have Dr. Cunningham explain the clinical data on that.

DR. POGGIO: This actually connects with what I mentioned at the beginning when I said there was one exception to when we discontinued the patient to explanation. We did for all of the analyses except for these analyses where we actually used that as the data, if you will, as a baseline for the next set of patients.

So I'll run through this focusing on the saline perspective part, but revision patients are basically defined by the FDA as patients that are replacing their original implant regardless of whether your original implant was for augmentation or reconstruction.

And in the saline prospective study -- and I must apologize here. The 196 is actually the number of devices. It's 124 patients, and the 215 in the large, simple trial is, indeed, the number of

patients.

Next slide.

This slide showed the complication rates in the LST for revision patients with 95 percent confidence intervals, in the "large simple trial," I should say, and this is on a per patient basis at 12 months.

And the next slide.

And now we're looking on a per device basis at 36 months, and we did actually so that we have the estimated rates for the major complications here with 95 percent confidence intervals, and we tested whether there was a significant difference between -- and I'm sorry. This is for prior, where the previous implant was for augmentation. The next slide is the reconstruction.

We compared whether there was a statistically significant difference between these estimated rates and the rates per the original augmentation, and there was no significant difference with the exception of explantation, which was somewhat higher.

Next.

And then for reconstruction, again, the same five major complications with estimated rates, complication rates, and 95 percent confidence intervals, and again tested for significant difference between this, and in this case the original reconstruction, and we have two significant differences, one up and one down.

And then we also have information on effectiveness, and I think I'd rather turn that over to Dr. --

MR. PURKAIT: -- show the complication rate and then Dr. Anderson will show the effectiveness.

MR. POGGIO: Okay.

DR. CUNNINGHAM: It was of interest to me to try to determine or theorize why these rates of clinically significant changes in these patient cohorts over their primary indication for implantation, and to come up with a clinical story that explains it.

The explantation group, which is higher

after the revision, the causes for explantation, the second explantation, are capsular contracture, deflation, and infection, and I think what we're seeing here is a group of patients who had an intervention to try to solve a problem. They had a capsular contracture. They had some other problem and had an implant placed in an attempt to solve that problem.

And I think this increased explantation rate shows that the problem was attempted to be solved, but was not, in effect, solved. So a patient who in a clinical situation, as we were discussing earlier, might have the signs and symptoms of a cellulitis, you try to deal with it with intravenous or oral antibiotics. It does not resolve. You offer the patient the choice.

The choices are: we remove your device, let you have no device for a period of time while you heal, and then replace the device. That's one option that we offer patients.

Another option that we offer patients is we can go in, we can take out the infected device, we

can clean the space, we can put you on oral antibiotics or IV antibiotics, and we can try and save you a third operation or another operation and put the implant back in at this time.

And I think what we're seeing here is that there are times where we try to do that and were not successful.

With respect to the reconstruction patients, I think the decreased number of capsular contracture Baker Grade III or IV that we see after reimplantation indicates the opposite story, but this is a group of patients where we were able to successfully treat a problem, namely, that of capsular contracture, by operating on the patient, taking out the scar capsule contracture, dividing through the scar capsule, whatever, and that this decreased number indicates we've been successful.

With respect to deflation, it's a more difficult question to answer for me clinically as to why this group has a slightly greater risk of deflation than when they originally had their device placed, and I feel that I have to come back to the

sense that it's a more adverse environment.

Perhaps if the surgery was done for a capsular contracture and the contracture continued to exist for some reason, we know that that might be associated with a greater incidence of rupture.

Now, the bigger question is: how do patients who have already undergone a frustrating experience? They've had high hopes of success. The operation has been done, and it hasn't worked out. They've had to have another implant placed. So a very significant question is: how do they take this? How do they respond to it? What's their satisfaction level?

And I would like to ask Dr. Anderson to spend a second or two talking about that.

DR. ANDERSON: We had used the breast evaluation questionnaire to assess patient satisfaction in the saline perspective study. So we decided to look at patient satisfaction in this revision group of augmentation patients on the three aspects, size, shape, and firmness.

And as you can see, despite the fact that

they experienced revision procedures, they still reported very high levels of satisfaction at the 36 months follow-up with respect to size, shape, and firmness.

CHAIRMAN WHALEN: Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: I believe --

CHAIRMAN WHALEN: Excuse me one second.

On that same issue?

PARTICIPANT: No.

CHAIRMAN WHALEN: We're going to someone else and then I'll get to you.

DR. BANDEEN-ROCHE: I believe my question series is for Dr. Anderson: concerns about the quality of life data, and certainly include the lack of a control group.

And so first of all, just correct me if I'm wrong, but my understanding is you really don't have any true quality of life data for the augmentation patients. It's body appearance and self-esteem data rather than quality of life, is it not?

DR. ANDERSON: I suppose you could characterize it as body image.

DR. BANDEEN-ROCHE: Okay. In terms of the slight increase of self-esteem, I'll just voice my concerns, and I just want you to respond. If women went into the surgery at a particularly low point of their self-esteem, which is certainly reasonable, slight increase would be consistent with regression to the mean, wouldn't it?

DR. ANDERSON: I'm not a statistician, but, yes, I understand the concept you're talking about, and that's probably true.

Are you referring to the Tennessee self-concept scale?

DR. BANDEEN-ROCHE: Yes, I am.

DR. ANDERSON: Okay. With respect to that scale, we've acknowledged that that scale is maybe not the best assessment to have been utilized, and that's one of the reasons I didn't present it in my presentation, even though we did achieve clinical significance. We didn't know if the results were -- I mean statistical significance -- we didn't know if the result were clinically meaningful.

DR. BANDEEN-ROCHE: Okay. Thank you.

My next question goes to the reconstruction patients. So you noted increases in quality of life on the FLIC. I'm just going to state something, and just correct me.

My impression is that those increases are not distinguishable from increases that could have happened anyway just because they've recovered from their cancer.

DR. ANDERSON: It's very possibly true that they would have over a period of three years adjusted to their cancer and shown an improvement. In my clinical experience, however, I do see that there is a tremendous amount of satisfaction with restoration of the breast in these patients.

DR. BANDEEN-ROCHE: Thank you.

CHAIRMAN WHALEN: Ms Brinkman.

MS. BRINKMAN: Yeah. Along that same vein, I'm interested in your Beck depression inventory because in reconstruction patients, you say, you know, that their scores have decreased, but, I mean, is that a decrease, and how do you know the difference whether it's a decrease due to the fact that they've finished

cancer therapy treatment or whether it's actually the fact that they've had an implant?

How do you separate that?

DR. ANDERSON: Well, you know, it was relatively nice to see that they weren't a real depressed group of patients to start with, which is consistent with one of my studies, which looked at psychological adjustment in breast reconstruction patients, and I suppose that it is theoretically possible that levels of depression would have decreased over time in these patients.

Again, I relate to my clinical experience. These patients are overwhelmingly satisfied and pleased to wake up from surgery with a breast mound.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: I wasn't going to open the door to Betadine, Dr. Cunningham, but it's already been opened, and I think I have to walk through it.

My recollection is that Mentor initially sent out a flyer to users of breast implants saying that Betadine was a problem with the integrity of the implant, and that was from a study in which Betadine

had been placed within the device, and the problem at that time was a valve failure.

And then there was some furor about it within the plastic surgery community, and as I recall, Mentor did another study or perhaps a parallel study with the implant immersed in Betadine solution and found no problems with that in vitro.

Now, is my memory of that correct?

MR. PURKAIT: Some of them, correct, and some of them -- if I may have your indulgence, I'd like to kind of go and kind of give this.

When we looked into the Betadine, this was brought to our attention by many different surgeons. They are the one who called us and said, "Look. Maybe you should take a look at it because some of the implants are showing failure because of some reason we do not know."

Well, when we started looking into their information and the data, we realized that there was a large amount of Betadine was used with our implants in all conditions, whether it has been soaked or put inside the cavity or put inside the implant.

We initiated our internal investigation and studies to understand was there any relationship between the Betadine and the implant failure. We have done several experiments three different times, one with the solution inside, one with the soaking, and also to match up the acidity of this particular one to make sure that the acidity doesn't have anything to do with it.

So the series of experiments have indicated that, one, either the implant does fail even with the contact, and when we learned that --

DR. BURKHARDT: I'm sorry. I didn't understand when you said that. That the implant does fail?

MR. PURKAIT: Failed, yes. The implant failed. When I said "failed," it means the pads tends to come out of the shell or the shell itself, the surface of the shell looks like getting weaker, and you can easily probably break through that. Those are the kind of observations we have seen.

And when we saw that, we realized that any way we want to do it -- in other words, if we can go

back and probably do some more experiments to tease out exactly what conditions and what time, we kind of felt that this is our responsibility to contact the agency with that information, and we did so, and at that point in time, the agency and ourselves decided that we should put that immediately with the patient information, with information that with even the slightest contact will provide or will probably fail or show the loss of integrity of the implant in the future.

So that's where it is.

DR. BURKHARDT: For Dr. Cunningham, were the failures that you observed with the Betadine irrigation, were they valve failures or were they the usual fold flaw failure, or do you know?

MR. PURKAIT: We have the failure, the deflation, as we have shown you before. We only saw two fold flaw failure. We did see some failure because of the tear of the shell. That's the largest number.

Now, it's very difficult sometimes to exactly identify the tear was already there or it was

the loss of the shell thickness for some reason. So we couldn't really identify that very well.

DR. BURKHARDT: Thank you very much.

CHAIRMAN WHALEN: Dr. Morykwas.

DR. MORYKWAS: I just wanted to ask a follow-up question of Dr. Cunningham on the infection that I brought up before, and just to simplify things, I'll say an early infection is one that is apparent before the incision is totally healed, and a late infection is one after the incision is healed.

Do you have the percentage of early versus late, and was it at all correlated to the surface type of the implant, the smooth versus textured?

And I guess as a follow-up, did you use any of the partially textured implants?

MR. PURKAIT: The last question first. Partially textured implant was not used to understand that phenomenon, but as far as the breakdown of those, we'll talk to Dr. Gene Poggio to see if he can tease out the information for you.

DR. MORYKWAS: Okay.

DR. POGGIO: I can answer part of your

question pretty readily. Looking overall, across augmentation and reconstruction, and I have it separately for those if you'd like, in the first year -- this is using the Kaplan-Meier estimates and looking at changes from year to year. So how much happened in the first year and then how much increased; did it increase between the end of the first year and the end of the second year?

So infection overall, 2.8 percent in the first year, 0.5 percent in the second year, and 0.16 percent in the third year. So it's almost all in the first year.

DR. CUNNINGHAM: But in terms of teasing out, I mean you're asking for a time frame of one or two weeks, and the first interval follow-up were data reported as four to six weeks, and these would presumably be detected earlier than that, but they would be, you know reported as they accumulated.

I think in clinical practice they occur most frequently within the first two weeks, and it's a little bit different than a wound infection without a device because most plastic surgeons, as Dr.

Burkhardt has teased out, try to use antibiotics, Betadine, whatever they can, to make this complication go as close to zero as possible.

So there are times where the -- plus giving prophylactic antibiotics -- so there are times where the time course is shifted or delayed out into the future than in a wound where there is, you know, no prophylactic antibiotic, not as much irrigation, but clinically my impression is that they almost all are most apparent within the first two to three weeks, and it's very rare that you see a late complication associated with, say, some dental procedure or some other seeding.

Here's the time to occurrence. Four to six weeks is 53 percent, which is the majority. Six months is 24 percent. Twelve months is 17 percent for reconstruction patients, and then in terms of the infection by device, the textured device, both the SILTEX and the SPECTRUM, are more likely -- it looks like about 85 to 90 percent -- are more likely to have an infection.

CHAIRMAN WHALEN: Dr. Change.

DR. CHANG: I'm going to quote Dr. Burkhardt again because it is my concern that on the face of it, although in the ten year retrospective study patient satisfaction rate was high, 93 percent, could you help me out? And I presume you're looking at infection, significant capsular contracture and deflation rate. Could you help me out and in your own words, how would you explain to a consumer, to a patient that despite one in four complication rate at ten years, that this is, indeed, a safe product?

Overall complication rate is 27 percent.

DR. CUNNINGHAM: I can speak to, you know, what I see clinically, and perhaps Dr. Anderson can speak to that as well.

First of all, no plastic surgeon wants a surprised or unhappy patient, particularly when we're doing elective surgery, aesthetic surgery. So I think one of the ways to explain the fact that despite a one in four risk for complication or reoperation patients are generally satisfied goes to the degree to which they are informed.

If I as a plastic surgeon whitewash the

possible complications and have the kind of risk of complications that we've demonstrated today, I'm going to have a lot of very unhappy, surprised patients saying, "How could this happen to me?"

Whereas if I go as far as I can to stress what the risks are, make clear what things could go wrong, and make clear that the patient understands that and we're not pretending that it's not going to happen to them, we're saying it could happen to you; I think that sets an expectation set that makes anything that does occur more acceptable to a patient and not something that's going to diminish their overall result.

But I think when we ask the patients to rate themselves on a strongly dissatisfied, dissatisfied, satisfied, very satisfied -- I can't remember what the fifth one was -- the vast majority of them also when we asked them would you do it again, the 90 percent range was, yes, they would.

So I think part of it is they're well informed, and so they tolerate the complications.

CHAIRMAN WHALEN: Ms. Dubler.

MS. DUBLER: I'd like to pursue that just a little bit because I have an epistemological problem. In the context of research where IRBs have to weigh the risk and benefit, there's an articulate, although not the majority of scholars who argue that the informed consent process can cure the defects in the risk-benefit ratio; that it doesn't really matter what the risk-benefit ratio is. If you can tell the patient and the patient can make an informed choice, it solves your problem.

But in the context of the FDA's finding that something is safe and effective, I'm not sure that an informed consent response solves the underlying problem. So we have a 27.6 overall complication rate.

I don't know. I think women want it. I think they're satisfied. Your data seems to show that, but I don't know how we can find it safe. Now, maybe that's a question for the company. Maybe it's a question for the FDA, but that's a problem for me.

DR. CUNNINGHAM: Well, I think --

(Applause.)

DR. CUNNINGHAM: You know, I think we wouldn't want to try to make the assessment for the patient. We are constantly asking them what their assessment is. That's the basis of the data that Dr. Anderson presented. It's the basis of the data that I presented.

I think there are two different risk-benefit sets. There's obviously a different set for the augmentation patient versus the one for the reconstruction patient.

I think another thing that we haven't really talked about extensively here is that we're not just counting pieces of chalk marking on a blackboard. The complications that we talk about, some of them are significant and impact definitely on a patient's life, and some of them are things that they can control and determine themselves.

For instance, the patient who wants to change their size is recorded as a reoperation, but it's not an obligatory reoperation. It's something that they choose to do to improve their result.

So it's not exactly the same model as some

of the others that you might be looking at because the patient is in so much control of the process relative to, you know, you need a heart valve, you need a pacemaker, this you need. It's a different situation.

A lot of these operations are things that patients choose to do.

CHAIRMAN WHALEN: Dr. Burkhardt.

DR. BURKHARDT: Yes. Dr. Cunningham, I forget exactly what the figures were. Seventy-two of 88 implants that were removed were replaced at the same time, and the problem was apparently size. So rather than being a concern about the integrity of the device or anything, it does raise some question about how the size is picked in the first place.

How did you do that in your study?

DR. CUNNINGHAM: I think we left the size determination to the surgeon's individual practice. There's no way that the company could help the surgeon decide what size the patient would need for the patient to be happy, and I think certainly I have seen in my own clinical practice where a patient might come in with one set of expectations before they have any

surgery, and then as time goes on, their expectations and their desires change after the operation.

So there are times when patients come in and demonstrate or discuss a certain look or appearance, and then after the surgery they say, you know, "I would like to enhance that further," and that's part of what we see when the implants are changed, particularly for a larger size.

DR. BURKHARDT: I guess my point would be that as I understand it, then that doesn't reflect deficiency of any sort on the implant, only in the decision making process as to the size originally.

DR. CUNNINGHAM: I think what you're reflecting is a communication issue or a change in communication or change in desire on the part of the patient, not an implant related problem.

DR. BURKHARDT: Thank you.

MS. DUBLER: Could I follow up with that, please?

CHAIRMAN WHALEN: Yes.

MS. DUBLER: I just want to follow up this discussion because I think it's very interesting, and

that is the Betadine discussion and perhaps the reoperation to put in a larger prosthesis reflects on the quality of the practice of the surgeons more than it does on the device itself.

So, again, it's hard for me to separate out how much of this reoperation and overall complication rate is related to the device and how much of it is related to surgical patterns of practice, and how we allocate or understand that I think makes a difference in this context.

DR. CUNNINGHAM: I take that as more of a statement than a question.

MS. DUBLER: Okay.

MS. BRINKMAN: I just have one question. You're talking about your ten year study, your follow-up. You're using the SEER data for that?

MR. PURKAIT: That's what the cancer patients primary.

MS. BRINKMAN: And that sample size is a little over 200? That's about it, of saline?

MR. PURKAIT: No.

DR. CUNNINGHAM: No, the ten year data

that I presented is not the SEER data. The SEER data was another part of the way of looking at the reconstructed patients and what their failure rate was, their deflation rate.

MS. BRINKMAN: But in the SEER data, the saline implant population number was about a couple hundred for the reconstruction?

DR. CUNNINGHAM: That data set, I think, was complicated by the fact that it was a retrospective study. A lot of charts were looked at, and there were definite incidences, and perhaps Dr. Poggio or one of the others can pull that out, where devices were recorded as implants, but clearly as you look back over the medical record, they were not ever meant to be permanent devices. They were soft tissue expanders, not implants.

So I think the large number of those that were soft tissue expanders and not implants kind of clouds that whole data set for us and it makes us very hard for us to interpret what is the actual failure rate in the SEER data for reconstruction patients.

CHAIRMAN WHALEN: Are there other members

of the panel who have questions for the sponsor?

PARTICIPANT: One quick one.

CHAIRMAN WHALEN: Well, I'm asking only because I've been asked to move the rest of the questions to a later point in time, but if indeed, we're done, we're done. But if there are others, we are going to move on now to the FDA presentation, and there will be time later for more sponsor questions, which I would project, looking at the schedule, should be some time before 2:00 a.m.

(Laughter.)

CHAIRMAN WHALEN: So we will move on to the FDA presentation, and I thank the sponsor for their presentation.

For all my fellow panel members, as the FDA is coming up for their presentation, please be aware it is past 5:00 p.m. We now are on overtime, which means that Jim Dillard will thank us twice on Friday instead of once for our work.

PARTICIPANT: -- other questions later on?

CHAIRMAN WHALEN: Not at the table, sir, because the FDA will be coming up, but please if you

could stay in this vicinity, that would be good because there will be questions, and also you have a summation period later on.

(Pause in proceedings.)

DR. BERKOWITZ: I'll present the FDA presentation of the Mentor saline filled and SPECTRUM saline filled breast implants.

I'm David Berkowitz, the lead reviewer, and I will give an overview of the status of the preclinical testing, and then I'll finish with a one slide summary of the medical device reports for the Mentor prostheses.

And then we'll hear from Sahar Dawisha, who is the clinical reviewer and will review the clinical results.

And then we'll hear from Phyllis Silverman, who is the statistical reviewer.

To describe the device first, the saline filled device is available in six styles. The styles are determined by two things. One is the shape, like the round, the profile or the contour, and the other is the nature of the surface. The surface is either

smooth or textured, and SILTEX is the Mentor name for textured. So SILTEX implies textured, and the surfaces are either smooth, SILTEX or SILTEX PT, which is a partially textured device.

The saline filled device has a diaphragm, an anterior diaphragm valve, and of course, it's filled with physiological saline, and both devices, obviously the shells are made from silicone elastomers.

The SPECTRUM device differs from the saline filled device in that it can be postoperatively adjusted. The volume can be postoperatively adjusted, and when the desired volume is reached, the little valve for postoperative filling can be removed under local anesthesia.

The SPECTRUM device has a posterior kink plug value, and like the saline filled, obviously the filler is also saline.

The indications for use are augmentation, reconstruction, asymmetry, ptosis, aplasia, hypoplasia of the breast, replacement, and combined breast and chest wall deformities.

Mentor has done extensive chemical analyses on the device. They've looked at the levels of the volatiles, extractables, and metals, and these are important because, one, they characterize the materials present in the device and, secondly, they determine what is there and how quickly those things can diffuse out of the device to cause either local or systemic toxicity.

These are some of the toxicology testing. The pharmacokinetics testing came from the literature, but also relied upon the chemical determinations sine by knowing how much is present and how much could leak out, we know what the dangers are.

So, in fact, it turns out in terms of systemic toxicity, even if all of the low molecular weight components present in the device leaked out immediately, it would still be a wide margin of safety between the levels, say, the blood levels obtained and the toxic levels.

The middle group of things that were determined are all the, I think, quite commonly done biocompatibility things that are tested on most

devices, and I just want to mention at the end that the immunotoxicity is important for these devices, and it was quite extensive.

That is, in addition to doing simply the hematology and counting cells, they enumerated, you know, the B and the T cells and the T cell subsets. They enumerated the killer cells, for example, and they also estimated the effects of implanted shell material on killer cell activity and on things like the mixed leukocyte response.

So various aspects of the immunology were broadly tested.

The remaining, these toxicological things have to do with mutagenesis and in bacterial testing and in mammalian cells, and finally culminating in a two year rat carcinogenicity study which demonstrated no carcinogenicity.

The company also did a reproductive toxicology and teratology study, and that was also negative, which would have been expected.

The mechanical testing, on the other hand, is not complete. Mentor has done some mechanical

testing on each of these topics, and we have also received some recent data which have not yet been reviewed. But with all the testing we now have, we think that the data are not yet sufficient to make a recommendation for all the implant styles proposed in the PMA.

So we are still going back and forth with Mentor on the mechanical testing.

Finally now, to change topics, I'd like to put up a slide summarizing the medical device reporting for Mentor, and this slide summarizes the medical device reports that FDA has received for the Mentor saline filled breast implants during the last three year period.

The first column, that is the Maude reports -- oops, I missed the slide -- the first column, the Maude reports, the Maude system received reports directly from patients, health care providers, practitioners, and from manufacturers.

The second column lists the five most frequently reported adverse events that are reported in summary form by Mentor on a quarterly basis. So

these are the sums of the reports for the last -- for over the three years shown above.

So that's all I'll say about this, and I think now I'll ask Dr. Dawisha to come and begin the clinical report.

DR. DAWISHA: Good afternoon. I am Sahar Dawisha, a Medical Officer in the Division of General and Restorative Devices, and I will be presenting FDA's clinical perspective of the information provided in the Mentor Corporation's saline filled breast implant PMA.

The clinical studies reported in the PMA are summarized on this slide and consist of a retrospective assessment of implant removal from the SEER data base, a one year large, simple trial, or LST; the saline prospective study, or SPS; and the Mentor retrospective study.

The SEER and LST were conducted in response to suggestions from FDA in 1994 on the type of information needed for PMA approval submission. The SPS is a prospective clinical study which was approved by FDA in 1995 after all augmentation and

some reconstruction patients had already been enrolled.

Because the saline prospective study contains the main safety and effectiveness information, I will focus on this study summarizing the SEER and LST only briefly. I will not be discussing the Mentor retrospective study because the patient population in this study is highly selected and because data ascertainment bias severely limits the conclusions drawn from this study.

The sponsor funded a retrospective analysis of implant removal in a breast cancer population cohort from the surveillance epidemiology and end results or SEER program of the National Cancer Institute because they were having difficulty enrolling reconstruction patients in their clinical studies. Women with a diagnosis of breast cancer in the years of 1983, '85, '87, and '89 with any type of breast implant, including silicone gel filled, saline filled, and tissue expanders, were asked to respond to a questionnaire regarding implant removal.

The results of this study are shown here.

The nonresponse rate was 20 percent overall. Of the 1,375 total implants removed -- I'm sorry. Of the 1,375 total implants, 32 percent were removed.

Of the 252 saline implants, 43 percent were removed.

There was information provided based on the reason for removal, and excluding the 28 saline implants removed as part of planned reconstruction -- these are the tissue expanders that Dr. Cunningham was referring to -- the reasons for saline implant removal are shown.

Capsular contracture constituted the single most common reason for implant removal, 35 percent of implant removal.

The large, simple trial was designed as a prospective study of a large number of patients followed only for the safety endpoints of capsular contracture, infection, rupture, deflation, and explantation for a total of one year. The sample size of 3,000, and 5,000 patients was proposed by the sponsor to estimate complication rates with a precision of one to two percent.

The LST results at one year are shown here on a by patient basis. The analysis method used here is the Kaplan-Meier survival analysis, which shows a risk of a first occurrence of a complication, along with a 95 percent confidence interval, which is shown in parentheses.

Not that for the total group, which is in this column, the confidence interval are all within one to two percent as proposed by the sponsor. However, the intervals for the reconstruction and revision patients are much larger, and in some cases there was insufficient information to estimate the proportion.

There were a total of 2,373 patients enroll with the majority as augmentation, and the follow-up rate at one year was approximately 47 percent.

Of the four complications studied here, capsular contracture, Baker Grade III or IV was generally the complication encountered with the greatest overall frequency.

Furthermore, you can see that for the two

complications in which there was sufficient information, which would be explant and capsular contracture Grade III or IV, the revision patients generally have rates between those of augmentation and reconstruction.

With the exception of this study and the implants in the SPS in which there was replacement and follow-up information, the sponsor has not collected safety and effectiveness information on revision patients.

You'll be asking the panel questions to discuss the revision indication.

Before I discuss the SPS in detail, I would like to show you the implant style studied in Mentor Corporation's clinical studies, as well as those not studied for which the sponsor is seeking approval.

Note that the sponsor is no longer manufacturing implants with an oval shape or with a leaf valve. The implants with a contour profile shape have a greater contouring than those that are contoured, and the major difference here is the

partially textured devices. These implants appear to be unique from all others in that they are textured only on the posterior surface. The texturing is more pronounced. The posterior textured layer is an additional vulcanized layer, and this layer is made from a different, softer silicone.

The sponsor has been asked to clarify how this new texturing differs from the type of texturing in their clinical studies and to explain whether and how the clinical performance can be inferred from this new texturing method.

The saline prospective study was initiated in 1993 and approved in 1995 after augmentation and summary construction patient enrollment. The study is a prospective, open label, multi-center study with three years of total follow-up for patients seeking primary augmentation and primary reconstruction.

Safety was based on local complications, and effectiveness was based on breast dimension changes, patient satisfaction, and quality of life measures.

The sponsor collected lactation and

reproduction history at baseline and connective tissue disease, or CTD, symptomatology and breast conditions at baseline and at follow-up.

A sample size of 1,200 to 1,500 patients with at least 20 percent of these as reconstruction was proposed to estimate the 95 percent confidence interval precision for complications.

The patient disposition at three years is shown here. Of the 1,265 augmentation patients enrolled, approximately 76 percent completed their three year visit. For reconstruction, the completion rate was 66 percent at three years.

Of the patients who were withdrawn, the majority for augmentation were lost to follow-up. For the majority of reconstruction patients who were withdrawn, the majority were explanted. The 15 patient deaths reported in this study were not implant related. For the 49 augmentation and 75 reconstruction patients who underwent explantation, subsequent complications are not included in the Kaplan-Meier complication rates to follow.

The three year cumulative Kaplan-Meier

rates of first occurred and 95 percent confidence intervals for selected complications are shown here on a per patient basis for the patients in the saline prospective study. You can see that the largest 95 confidence intervals are plus or minus three points for augmentation and plus or minus five points for reconstruction.

Note that the capsular contracture shown here includes both Baker Grade III or IV and Baker Grade unknown or unreported, and that the category of any complication here includes reoperation.

The cumulative risk of a first occurrence of a complication is 43 and 73 percent, respectively, for augmentation and reconstruction. Although only the three year rate is shown here, the cumulative rate of first occurrence of any complication increases over time and has not leveled off by three years of follow-up.

The cumulative risk of at least one reoperation for any reason over the three year period is 13 percent for augmentation and 40 percent for reconstruction, and these rates, as well, are

increasing over time.

In general, the complication rates for reconstruction are three times greater than for augmentation.

The cumulative rates of first occurrence of leakage/deflation, implant removal, breast pain, wrinkling, and nipple changes, which includes both loss of nipple sensation and intense nipple sensitivity, are shown here as well.

The most common types of reoperation procedures performed through three years is shown here based on the number of procedures. Percentages do not sum to 100 because I have omitted infrequently performed procedures from this table.

There were 358 and 353 reoperation procedures performed in the augmentation and reconstruction patients, respectively, through three years. For the category of removal with replacement, I combined the following categories reported in the PMA: implant size exchange, secondary augmentation, replacement, and revision.

Scar/wound revision includes skin

adjustment and wound management. Capsule related procedures include capsulotomy and capsulectomy.

The most commonly performed procedure for augmentation patients was removal with replacement, 32 percent of the procedures performed in these patients. And for reconstruction, it was a capsule procedure, 28 percent of the procedures.

Not shown here are the nine implant removals without replacement and augmentation and 40 in reconstruction patients.

The information shown on this slide was provided subsequent to the PMA submission at the agency's request, and it shows the reasons for implant removal through three years on a by implant basis. If an implant was reported to have been removed for multiple reasons, the hierarchy for categorization into this table is shown in the footnote below the table.

Cosmesis includes asymmetry, ptosis, wrinkling, and scarring. Of the 136 augmentation and 116 reconstruction implants removed over the three years of follow-up, other than a patient request for

a size or shape change, the single most common reason for augmentation implant removal was due to leakage/deflation.

Twenty-three percent of all removed augmentation implants were due to leakage/deflation. Infection and capsular contracture constituted the most common reasons for reconstruction implant removal, each at 26 percent of all reconstruction implant removal.

For both augmentation and reconstruction, if you were to take the complications and sum those, you would see that the majority of implants were removed due to a complication rather than due to patient request for a size or shape change.

In an effort to characterize the complication rate in revision patients, the sponsor was asked to provide the cumulative Kaplan-Meier first occurrence complication rate on a by implant basis for those implants which were removed and replaced during the study and for which there was follow-up information.

This table summarizes this information

through three years of follow-up. Because the sample size and follow-up is lower than for the primary implantation in the SPS, the confidence interval for this table are much wider than reported for the primary implantation group.

Note that the capsular contracture here, as well as in the other table I showed you, includes both Baker Grade III/IV and Baker grade unknown or unreported, and the any complication category here includes reoperation.

The risk of a first occurrence of any complication for this group is similar for these implants compared to primary implantation. However, for the major complications of reoperation, implant removal, capsular contracture, and leakage deflation, the rates are higher than for primary implantation and lower than for primary reconstruction, which is similar to the revision complication rate reported in the LST.

For most other complication the rates are similar or lower than for primary implantation. You'll be asked to address a revision indication in

the panel questions.

The sponsor performed Cox regression analysis for several patient at implant variables which they showed you and for the complications of infection, capsular contracture, deflation, reoperation, and removal, and selected associations are shown on this slide.

There were no associations with infection. Implants with leaf valves had two times higher capsular contracture than those with diaphragm valves. Recall that the sponsor is no longer manufacturing implants with leaf valves.

Surgical pocket irrigation with Betadine was associated with a three and a half times greater risk of deflation than without,a nd implants with SPECTRUM valves were associated with a twofold higher risk of both implant removal and reoperation than those without.

With respect to other safety issues, the sponsor collected breast cancer and connective tissue disease information at baseline and at follow-up. Of note, there were two augmentation patients who

developed breast cancer during the course of the study, one patient two years and the other patient five months after implantation. At any follow-up visit complaints of fatigue, generalized achiness and/or joint pain were reported infrequently in patients without such a report at baseline.

There were six confirmed and 31 unconfirmed cases of connective tissue diseases reported over the course of the study. The six confirmed cases are shown here with the indications shown as well.

There were two patients with osteoarthritis and one with an undetermined arthritis and one with ankylosis spondylitis in the reconstruction group.

In the augmentation patients, there was one patient with systemic lupus erythematosus and rheumatoid arthritis reported during the course of the study.

Without a control group of sufficient numbers of similar types of patients followed for the same duration, conclusion regarding the association of

the CTDs shown here with these implants cannot be made.

With respect to effectiveness, the augmentation patients and delayed reconstruction patients experienced an increase in breast size. Augmentation patients were generally satisfied, and they experienced small, but statistically significant improvements in one of the ten subscales of the multidimensional body self-relations questionnaire, or MBSRQ, and small but statistically significant improvements in the Tennessee self-concepts scale.

Reconstruction patients experienced statistical improvements in the functional living index of cancer scale, or FLIC, and immediate mastectomy patients experienced improvements in the Beck depression inventory.

There were no statistical improvements in the MBSRQ or in the Tennessee self-concept scale for reconstruction patients.

Recall that the SPS was initiated in 1993 prior to FDA approval in 1995. Shortly after FDA approval, the sponsor was informed that continued

follow-up beyond three years would be advisable. The sponsor contacted patients who were still participating in the SPS at that time to solicit continued follow-up in the form of a yearly postcard assessing for deflation.

Of the 1,045 augmentation patients in the SPS at that time, 519 or 50 percent agreed to the four to ten year follow-up. Of these 519, 362 patients returned postcards, a 70 percent response rate, and in these 362, there were 36 deflations reported or a rate of ten percent.

Of the 375 reconstruction patients in the SPS at this time, 186, or 45 percent, agreed to the four to ten year follow-up. Of the 186, 144 returned their postcards, an 86 percent response rate, and deflation was reported in 17, or 12 percent, of these patients.

You'll be asked in the panel questions to address the duration and type of follow-up information needed to fully characterize the long term safety of these implants.

In summary, the cumulative risk of a first

occurrence -- of a first complication is 43 percent for augmentation and 73 percent for reconstruction; is increasing with time; and has not leveled off by three years.

Cumulative complication rates of reoperation and removal have not leveled off as well at three years.

Although cumulative local complication rates are increasing, the types of local complications are well characterized, and the rates are precisely defined. In augmentation patients, most reoperations are implant removal. For both augmentation and reconstruction, most implants are removed due to a complication rather than due to a patient request for a size or shape change.

Breast size benefits were realized for augmentations and quality of life changes were evident, but small. For reconstruction patients, quality of life measures generally improved.

You will be asked to discuss these safety and effectiveness issues in the panel questions to follow.

Thank you.

I'd like to now introduce Ms. Phyllis Silverman, who will be discussing the statistical perspective.

MS. SILVERMAN: Good afternoon, or perhaps I should say good evening. I'm Phyllis Silverman, the statistical reviewer for the Mentor PMA.

The statistical sections of this PMA are well written, comprehensive, and address nearly all of the requests put forth in the draft guidance for breast implants. The sponsor's PMA contains safety and effectiveness data from five studies.

Since the saline prospective study is the only one that utilizes the device in question, includes all of the endpoints of interest, and fulfills the recommended follow-up, I consider it to be the primary study, with the others lending various degrees of support.

Because of the approximate 50 percent loss to follow-up with the large, simple trial, the ability to draw meaningful conclusions from this trial is limited. Therefore, my comments will focus on the

saline prospective study.

Because there was no control group and therefore no claims of superiority or equivalence, the safety and effectiveness results for this device must be evaluated by way of descriptive statistics. Complication rates, implant survival curves, and effectiveness parameters must be evaluated from a clinical perspective.

As a statistician, my role is not to judge the acceptability of these rates, but to evaluate the validity of the data presentation as well as point out any weaknesses in the study design and analysis. I will start with some comments on sample size.

Because there were no null and alternative hypotheses for the primary endpoints, hence making statistical power a non-issue, the adequacy of the sample size was determined by the desired precision around the estimates of complication and reoperation rates. The larger the sample size, the smaller the width of the 95 percent confidence intervals which are used to represent the precision.

We wanted to insure that the width of the

confidence intervals would be no more than about plus or minus four and a half percent when rates were high, for example, a 40 or 50 percent complication rate, and only about one to two percent when rates were low.

The sponsor's enrollment of 1,265 augmentation patients and 425 reconstruction patients resulted in a three year accountability sufficient to meet this precision. Therefore, I feel the sample size was adequate.

This brings me to the Kaplan-Meier curve. The sponsor used Kaplan-Meier curves to estimate the occurrence of complications and adverse events. This technique allows women who were not followed for the entire three years to contribute information to the, quote, survival curve for the time that they were in the study. They either experienced the event in question or they are, quote, censored at their last follow-up, which means they are dropped from the denominator at that point.

I feel that this is the best technique that the sponsor could have used for this type of data. There are, however, three weaknesses with this

methodology as applied to these particular data. The information collected reflects prevalence and not incidence, and thus, new cases of infection or contracture, for example, could not be distinguished from continuing cases.

Therefore, survival curves are based on the time to the first occurrence of each complication and multiple occurrences could not be analyzed.

Secondly, because a patient explanted or revised will be censored from the table and not be in the pool to experience other complications, there is the issue of competing risks which can add an uncalculated bias to these rates.

And, thirdly, with the exception of deflation, explant, and reoperation, the exact time of onset of a complication could not be known, but would generally have been noted at the next scheduled follow-up.

This interval censoring as it is called can add an additional unknown bias to the data. Therefore, the curves are not as exact as if one were measuring an endpoint like mortality in days.

A summary of the Kaplan-Meier rates for the primary safety endpoints is reiterated on the next slide. It can be seen from the table that the complication rates in the reconstruction group are about three times what they are in the augmentation group. Because of considerable difference between the augmentation and reconstruction cohorts, these rates must be considered separately by indication and evaluated from a risk-benefit perspective.

Is a three year explant rate of almost 27 percent or a re-op. rate of 40 percent acceptable for re-com. patients? As you can see from the slide, the 95 percent confidence intervals were plus or minus two percent or less for the augmentation patients and plus or minus three to five percent for the reconstruction patients. This is consistent with the guidelines.

Now, I would like to discuss some possible biases with the data. There are several sources of possible bias with this data. With three year follow-up missing for approximately 25 percent of the cohort, there could be a non-respondent bias in that women who were having problems were more likely to return for

follow-up than those who were happy with their implants. This would result in an overestimation of complication rate, or there could be the opposite scenario. Patients with complications were not returning for follow-up because they were seeking help elsewhere. This would result in an under estimation of complication rates.

A key assumption for the Kaplan-Meier analysis is that the censoring distribution is independent of the survival distribution. What this means in English is that whether or not a patient returns for follow-up should be unrelated to their level of satisfaction with their implants.

Since we do not know to what degree this is true or the reasons for patients not returning, we cannot ascertain this bias. We can only acknowledge that there probably is some, and the complication rates must be evaluated with this in mind.

Because many of the complications are self-reported, there is likely also to be some recall bias, especially with the reporting of connective tissue disease and the rheumatology screening. This

bias could go either way. That is, it could inflate or decrease the rates, depending on how a patient's memory compares to reality.

This is a weakness of a study design where follow-ups are infrequent and medical conditions are not always confirmed by a physician.

The last bias I wish to discuss is investigator or site bias. With a study design of 153 sites, it is virtually impossible to justify pooling on a statistical basis, and the sponsor did not attempt it.

Although there is always the possibility for difference in follow-up or results among sites, I feel that any site or investigator bias would probably be minimal, especially compared to some of the other variables that emerged as related to outcome.

For example, surgical approach, valve type, and implant shape are significantly associated with contracture, and valve type is also associated with explant and reoperation.

Incision size and use of Betadine irrigation was significantly associated with

deflation. The sponsor presented an extensive analysis of co-variables, such as valve type, implant shape, laterality, incision size and surface type by use of Cox regression.

Surface type was not significantly associated with contracture, the very thing it was meant to reduce.

Of the three biases discussed, my belief is that the nonrespondent bias is of most concern, and that the other two are probably minimal. This brings me to effectiveness.

The sponsor presented a very thorough analysis of effectiveness by way of descriptive statistics resulting from numerous surveys administered and objective breast measurements.

In addition, before and after comparisons of some effectiveness endpoints showed statistically significant changes. However, I question the interpretation of the phrase "statistically significant increase in breast size." It does not appear to mean anything from a clinical perspective.

The data must be looked at in the broader

sense. The data indicate to me that even though there were some dissatisfied patients, breast implants are overall effective from both a physical and emotional perspective.

Conclusion. In summary, I found the data analysis presented in this PMA to be comprehensive. The sponsor's analysis was consistent with the methodologies laid out in the guidance. The complication rates must not be taken as exact, but rather as estimates subject to the biases discussed earlier.

I would like to close just by presenting a few more statistics. Because there could be multiple complications per patient, and even correlations between adverse events, for example, contracture and pain, I would like to leave you with the complication free rates at one, two, and three years. These rates are not subject to the problem of competing risk and would be of particular interest to a prospective patient in making an informed decision.

Although some complications are more serious than others, the data show the complications

are, indeed, frequent. Approximately 57 percent of augmentation patients are complication free at three years, as opposed to only 27 percent of reconstruction patients. If breast implants are deemed acceptable for market, women must be presented with these figures so they can make an informed decision from their own personal risk-benefit perspective.

Thank you for your attention.

CHAIRMAN WHALEN: Thank you, Ms. Silverman and the entire team.

Well, our next order of business would be to have the FDA entertain questions from the panel. We have a sort of unscheduled break that we must take because apparently part of this room is not reserved for this block of time. So we're all going to get a little bit closer, too.

So if we would please take a 15 minute break while they resize this room and hopefully that will be sufficient time for them to do what they have to do.

(Whereupon, at 5:53 p.m., a recess was taken, to reconvene at 6:15 p.m., in the same place.)

E-V-E-N-I-N-G S-E-S-S-I-O-N

(6:15 p.m.)

CHAIRMAN WHALEN: I would like to ask that at the real conclusion of the FDA presentation that Dr. Berkowitz review for us the FDA questions that are going to be posed to the panel as the next step.

DR. BERKOWITZ: Question one, while the sponsor provided no long term clinical data on their implant, fatigue testing and fold flaw testing provides some information in the long term rupture leakage of the implants. Please comment on the sponsor's methodology and results for each of these tests.

CHAIRMAN WHALEN: Dr. Berkowitz, if you could just read all of the questions, we're not going to go into the deliberation upon each one just yet.

DR. BERKOWITZ: All right. Question two, given the data for augmentation patients in the SPS and other data provided by the sponsor, is there reasonable insurance as defined in 21 CFR 860.7 that the product is both safe and effective for augmentation patients?

Question three says given the data for reconstruction patients in the SPS and the other information provided by the sponsor, is there reasonable assurance as defined in 21 CFR 860.7 that the product is both safe and effective for reconstruction patients.

Question four, with the exception of the LST one year follow-up and the implants in SPS in which there was continued follow-up after explantation, the sponsor has not collected safety and effectiveness information for the cohort of revision patients. Yet the sponsor proposes revision as an indication for use. Given that this cohort typically represents at least 30 percent of the patients presenting for breast implantation, please discuss whether there is sufficient safety and effectiveness data to include revision as an indication and whether the sponsor should evaluate the safety and effectiveness for revision patients as a condition of approval.

Please also comment on the information that would be useful to collect in a post approval

study.

Question five, given that the sponsor's data show increasing cumulative rates per year for the majority of complications for both reconstruction and augmentation patients, please comment on whether there is adequate follow-up data to characterize the frequency and types of long term adverse events.

Please address the following pertaining to long term adverse events: (a) the minimum duration of follow-up; (b) the type of visit, i.e., active or passive, and (c) which types of complications should be assessed.

Question six, the sponsor's SPS study was not designed to provide information in the following long term issues of pertinence to women with implants: one, the interference on the ability of screening mammography to detect tumors in breasts with implants; two, the interference with lactation; and, three, the effects on offspring from women with implants.

Please discuss whether the sponsor should evaluate these issues as a condition of approval. If so, please discuss the appropriate methods for

addressing these issues.

And the last question is: given the heterogeneity of surgical practices and post operative management of mammary implantation, please comment on the important issues which should be included in physician training.

CHAIRMAN WHALEN: Thank you.

We now, therefore, proceed to the panel discussion and review of FDA's seven questions, and we will start that off by having three of the panel members in specific areas as lead reviewers make comments in their areas of expertise. Those three will be Dr. Li in mechanical testing, Dr. Burkhardt on the clinical study, and Dr. Blumenstein on statistical considerations.

First, for mechanical testing, Dr. Li.

DR. LI: Thank you.

Let me first say as an overall comment that it appears that mechanical failure of this device in the form of leakage or rupture is one of the primary reasons for revision and reoperation, and this is purely a mechanical failure in my view of either

some combination of material, design and environment, and it's unfortunate that that's actually the one area that was the most incomplete in your PMA.

The FDA has done a nice job summarizing their comments regarding your testing in the deficiency letter I believe you have received, and in general I agree with virtually all of your comments, but let me highlight a couple of them, I think, that are more important perhaps than the others.

One is, I think, you need to provide data for all models that you intend to market and not just the ones that you have selected. This goes for all the sets of testing.

The other is that most of the data, as I understand it, was done with the material of construction that you refer to as PTC, RTC, silicone. Yet the final products are made with Sytech (phonetic) silicone, and although you make some comparisons of basic material property similarities, I believe this argument is insufficient to merely make a material swap in those raw material properties alone.

For instance, one of your own data points

suggests that, in fact, Sytech and PTC are not equivalent in terms of if you look at one of your numerous tables that showed the elongation and break strength of Sytech versus PTC on dry heat. The Sytech silicone actually has improved properties of elongation and break strength. However, if you do that same comparison and the components are gamma sterilized, the order is reversed, and in fact, the Sytech is less strong and has less elongation.

So certainly I think your claim that the materials are equivalent is not supported.

That raises an odd issue. It appears through the literature that you have one particular Model 1600 which apparently from my reading may or may not be gamma sterilized, which is a little confusing to me. I'm not sure when you choose to gamma sterilize it and when you choose not to gamma sterilize it, and this might be important because basically all of the gamma sterilized material properties are significantly less than those that were heat sterilized.

So my questions would be: why do you do

this? How do you decide when they're gamma sterilized and when they're not? And more importantly, does the physician at the end of the line know when he buys a 1600 component if it's gamma sterilized or not and that there's, in fact, a material property difference?

In a more general sense, the thing that I was most taken back is these implants have been around for decades and the leakage and deflation has always been a key complaint or indication for revision, but none of the testing actually directly addressed this particular mode of failure other than your fatigue test, which as you describe it, is a catastrophic failure under extremely high loads and high cycle, which is some indication of leakage, but certainly not any mirror of what happens clinically apparently in these leakage phenomena.

So on the fatigue testing, there is a high variation in your results. If I can just quote a couple of your numbers in general, for your Model 2600 of the 175 milliliters volume and an 80 pound load, your cycles to failure varied from 3,000-something to over 32,000-something, a factor of ten from the best

to the worst.

If you take that same model and do the 325 milliliter sample at 75 pounds, again you get about a factor of ten difference, from 16,000 for the worst to 126,000 for the best.

And lastly, if you take the Model 2400 at the same volume and load, it actually fails at 850 cycles rather than the thousands mentioned previously. So although your average graph looks very good, if you factor in the actual cycle fatigue for each individual product, there's at least a factor of ten from best to worst for every component, and then the gamma sterilized version, the 1600 which would be expected to have the worst values, is not done.

You do do a lifetime survivorship in a couple of different ways. I don't dispute the methodology. However, everybody should be reminded that that safety factor is for that particular test. So if the end use was, in fact, that kind of cyclic high speed loading in your test rig, then that safety factor would, in fact, be appropriate.

But I think it's undoubtedly true that

that particular mode of failure is not what happened clinically. So I think it's not supported at all that a safety factor is, in fact, carried over to the clinic.

A technical detail, I think, that carries through all of this is the variation of properties and final results as a function of the percent of fill. I couldn't see actually on your reports that I saw how you exactly filled each one. Were they filled to the same volume? Were they filled to the same pressure? I wasn't that exactly sure how that was done.

And also in subsequent device tests, there might be cases where the worst case scenario is a device that's under inflated, and in another test scenario, the worst case scenario might be where it's slightly over inflated, and I see no addressing of the issue of inflation percentage at all, and this actually might be one of the surgically related phenomena that Dr. Cunningham alluded to.

A bothersome thing on the load thing is this. It seems to be a belief by yourself and Dr. Cunningham that how the surgeon puts it in, in fact,

makes a difference on the outcome. In fact, there's even a general agreement that somehow that provides higher stresses. Maybe there's folds; maybe there isn't; maybe it's puncture; maybe it isn't. But absolutely none of those particular factors are addressed in any of your testing components, so basically remains anecdotal even after 30-plus years of use.

The other tests are -- I guess I don't know what to do with them. You do a static and dynamic rupture test, which is either dropping of weights on something or just squeezing it until it breaks, and those are interesting kind of device tests, but I'm not actually sure how clinically relevant either one of those particular tests are unless you're going to tell me car accidents are actually one of the reasons that some of those devices fail.

The abrasion test is even more peculiar. I'm not actually sure what the clinical consequence of where is. Are you projecting that the clinical consequence of where is that the device thins and,

therefore, is more likely to rupture or are you worried about where and the fact that it creates some kind of particulate debris that goes on to cause some kind of systemic effect?

But in either case neither one of those particular issues is addressed, and you also use a Tabor abrasion test for which panel they stick a flat piece of membrane on a device and then rub against it a very roughened surface. In the crudest sense, sometimes it's a piece of sandpaper, and again, it's a relatively crude test. They're only testing a portion of the device, and again, I don't really know what to do with the device, nor am I sure that particular method of where it is, again, clinically relevant.

The tear test let's me get into the area of retrieval analysis. Depending on what numbers we see, the number of devices that were deflated varies somewhere from maybe three percent to, you know, some relatively much higher number at the end. So even if it's a five percent deflation rate and you've implanted 500,000 of these, there's 25,000 retrieved

deflated devices somewhere, and I only see a report that you provide that looks at ten of these devices that were retrieved for either deflation and/or wear, which is a little confusing because you didn't tell me which of the ten were retrieved for deflation and which were wear, and I didn't know if the ones that you called wear were also deflated.

So be that as it may, you did look at where -- tried to assess where the flaws were that caused the leakage, and the short answer is they appear to be everywhere. They may or may not be around folds. Some of your retrieved implants had folds, permanent folds. Others did not.

In most cases the cracks that you associated with leakage were nowhere near the folds. There were a couple that were on the folds, but I don't know if this is just a statistical chance that that's where the crack and the fold happened to meet, but certainly you can have folds without leaks, and certainly you could have cracks in areas without folds.

So your tear testing was a cruder sense.

The cracks that you identified in retrieval run the size of hundreds of microns, very small, sometimes even microscopic sizes, but your tear test is relatively gross when we take a big piece of material and you just try to pull it apart.

So I'm not quite sure of the relevance of this more macroscopic tear test to the crack initiation or propagation that you've identified as failure modes in the retrieved implants.

So, again, you've done a lot of tear testing, but I actually have no idea how to relate that to the clinical situation, and you also tore it only in one direction, and multi-directional tears and then assessments of you might have survived the tear test, but I didn't see you look at the samples as closely as you looked at the retrieved devices to see if, in fact, you created creases or cracks that may not have failed as a tear, but may have caused pinholes or whatever bit enough to cause a leakage.

I'm almost done. Bear with me.

The next to the last item is this issue of fold flaw. I think it's certainly a reasonable

hypothesis that somehow that these permanent folds that end up in this device are somehow related to the failure, but it's an interesting thing.

If you take a brand new implant and try to fold it and you just fold it in half and let it go, the fold doesn't stay there. It goes away, but just because it's a piece of nice, resilient rubber, but in these retrieved devices, that fold line is often rigid and hard, which indicates either a chemical and/or structural change in material along that fold. That's why that fold is permanent as opposed to if you take a brand new implant, fold it up, do some kind of fatigue test. The chemistry and the structure of the two folds, I believe, are completely different.

So I'm not quite sure that the fold flaw tests, as difficult as they are to run, again, have a clinical relevance.

And then an item that I didn't put much weight to until today's discussion is what for lack of a better term let me call reverse diffusion. It seems as if somehow the inside of these bags get infected somehow and microorganisms find their way inside, and

perhaps a mechanism for that is there's got to be a way for the bacteria to get into the device.

One of the earlier speakers even suggested that the valve, in fact, might be two way in the sense that you can let liquid in as well as liquid out, but, again, I see none of your testing that addresses that.

So in summary, I would say that the testing you have done actually has been rather extensive as far as the number of samples and effort that you've put in, but unfortunately hasn't really helped me answer the question at all, is that will this implant leak; how often will it leak; where will it leak; and there's this big mystery in my mind of the mechanism of why the implants fail more in reconstruction than they do in the original augmentation.

There's got to be a biomechanical reason. This is a mechanical failure, and you ought to be able to define how that happens and develop a test to address that issue.

So in the end of it all, I believe that the FDA is correct in saying that the tests are

incomplete and they should be completed, and additionally I think the reoperation rate due to inflation -- I find if I carry it over to the devices I normally work with are alarmingly high.

To have a device fail in the two to three year period mechanically is extremely surprising, and it's also amazing to me that it seems to be tolerated as just something that you just have to live with in these implants, and I don't really see how the design and the materials change or the testing really addresses that issue.

Let me stop there.

CHAIRMAN WHALEN: Thank you, Dr. Li.

I should point out to all the panel members, lead reviewers and the rest of the panel, that this is the appropriate juncture when, if there are any further questions for the sponsor or any specific questions to the FDA presenters that these questions be raised.

That being said, there were probably too numerous to count questions, but some of them were rhetorical. Some of them were comments, and some of

them were questions that perhaps an answer is needed, and so with that preface specifically for you, Dr. Li, among those questions you raise or any others that you have, would you like to direct any question specifically to sponsor or FDA at this juncture?

DR. LI: Let's see. Well, I guess I would like to -- well, I'm not exactly sure because the question is kind of broad ended. I'm struggling with asking kind of a non -- all of my specific questions might be kind of trivial, and the big question I'm not sure we can get into.

CHAIRMAN WHALEN: Well, there also will be a closing summation, about ten minutes for each, the sponsor and the FDA, that we'll get to eventually where anything that has been raised during this discussion can be addressed, although no new data will be raised.

DR. LI: Let me ask one general question then.

MR. PURKAIT: (Inaudible.)

CHAIRMAN WHALEN: Well, the point I was making is if I were to say to you right now could you

answer each of his questions, we'd all have to get cots because it might take the night.

DR. LI: Well, let me ask you one general question then. Do you believe that with all the testing that you have provided that you can a priori determine what the leakage will be? Because you clearly have some idea of things that you think are important, for instance, surgical placement, just to bring up another issue, where the size of the incision that you at least feel anecdotally are related to the performance of the device.

Yet I was frustrated by that because you don't have a hard number, biomechanical data that says, you know, when you make the incision this small, the force goes up 30 percent and the stress goes up this high and this leads to this and this leads to that.

I really kind of -- I don't see that particular sequential kind of argument that we normally apply to a device failure and every other medical device that have been in being applied to this particular device.

So what makes you -- what gives you the confidence or the belief that if you change, for instance, as an example, from PTC to Sytech or from something to partially textured, which you have not clinically proven; what leads you factually to believe, other than your personal belief, but in terms of data that would you believe that the leakage rate is going to be the same, smaller or bigger than your previous device?

MR. PURKAIT: I think -- let me go try to see. You have about -- I don't know -- 15 different areas that you have questioned, which is quite interesting because you get me going for the next two hours I probably can do that, but let me see if I could summarize and try to answer those, the simple question first and then go to the complex one.

You asked a question about the differences between the sterilization of dry heat versus gamma. Right now we all do dry sterilization. So one issue about gamma is out right now.

Now, the question was: why did you do the gamma nd dry heat and how would one --

DR. LI: If it's out, you don't have to answer the question.

MR. PURKAIT: Okay. Good. So that was simple.

DR. LI: It's in the application though, as I understand it, right?

MR. PURKAIT: The second question you had about the PTC active versus --

DR. LI: Just to clarify that, I raised the issue of that particular one because it was highlighted and takes up many pages in your PMA application. So you're now withdrawing that particular --

MR. PURKAIT: No withdrawing. You see any manufacturer operation always have an optional sterilization procedure because you cannot rely upon one particular type of sterilization. We do qualify both dry heat and gamma sterilization, and as we have established the process, validation of the dry heat, we have converted all of the sterilization to dry heat.

In case that there be a need in the future

we probably will do gamma sterilization, but this is not a withdrawal of the gamma sterilization.

DR. LI: Well if you're going to do it at all, then I think you need to answer the questions.

MR. PURKAIT: The gamma sterilization and the dry heat sterilization, we have compared the data, and that has been submitted in the PMA, and if you look carefully in the PMA, you will see that the gamma sterilization does reduce to some extent the mechanical properties in comparison to dry heat.

However, the range of the properties, what we see by the gamma, is far superior to the expected results that we believe we are going by, such as the ASTM standards. For example, if you have a 350 percent elongation, that's what we kind of maintain. Our product shows consistently over 350 percent elongation.

You might question, well, what does this 350 percent elongation mean, you know. Remember in a body when you put this thing in a cavity, we have a liquid elastomer which goes up to 700 percent elasticity. Now, here we are testing for 350 percent.

In a body probably under all loads we know that we can measure, this probably wouldn't extend more than 20 percent to 30 percent.

So, you know, to look into the proper perspective, the elastomer elasticity in this case is much superior or much more higher than is reported in the body.

DR. LI: Well, let me stop you here. This is my general problem, I guess, with the testing. First of all, the ASTM methods for those of you who aren't into ASTM methods are proposed standard ways of doing tests, and there's not an ASTM method yet that I've read that doesn't have a disclaimer in there that if you meet these standards, it has nothing to do with projected clinical performance.

So if you followed the ASTM standard, you're basically telling me you're following a standard test, but as the ASTM itself says, it's not performance related.

And this is the general problem or concern I've got with all of your testing.

MR. PURKAIT: I understand that.

DR. LI: It performs to some standard, but I can't make the connection to the clinical case where maybe 19 percent are failing by leakage. Your tests suggest that.

MR. PURKAIT: I agree with you. The ASTM is not our Bible; that we follow ASTM, therefore, everything is good. The ASTM is a standard that's accepted across the country, across all product lines, all devices that exist. So we do follow their standard.

At the same time, we supplement many other tests to show that not only do we meet ASTM. We also have other tests to show that we go beyond that. So ASTM is not the only study that we do to say that our product --

DR. LI: I understand that, but at the end of the day, you still have a 19-plus percent, up to a 19 or more percent leakage rate.

MR. PURKAIT: Now you talk to my heart. If you look at the in vitro versus in vivo situation, unfortunately we are at a loss to exactly simulate what happened in the body process in vitro.

For example, you have seen in our data today that if somebody used Betadine, if somebody used different incision size, if somebody used a bilateral, if somebody used a different valve type, there are some clinical indications that will occur. A clinical problem will occur that it cannot replicate every time in vitro.

I'm not saying that we're not going to try for that. However, at this point in time we took into consideration the best we can, and we continue to study that all the time.

DR. LI: I'm not saying that you didn't do your best. What I'm saying is that there's a disconnect for me between the data you generated and the prediction of in vivo performance. I mean I'm not disputing the hard work that you put into it or you sincerity in doing --

MR. PURKAIT: Well, I'm not going to argue on that. I'm trying to make the point that some of the test conditions, what we have used, does have some real meaning behind it.

That includes one of the areas you also

have addressed the fact that our fold flaw or the leakage things -- let me address the leakage one.

To understand the deflation or leakage in a body, we considered that there are three ways, primarily three ways that it can fail: rupture of the shell, the valve failure, or maybe fold flaw, or maybe other reasons in the clinical.

The rupture in the shell, we try five testings, such as fatigue, the static rupture, the static impact, and so forth. For the valve competence, we have three different tests for valves. We have valve burst test. We have valve special test. We have valve -- the flow properties test.

For the fold flaw, we believe that the fold flaw test is very unpredictable because you cannot predict where and when, how the fold will be formed. That has a lot to do with how it has been implanted and how these devices have been put there.

And the other question I think previously asked about, the special inferences in different locations, initially all of these implants are folded and put inside the cavity and then has been placed and

then been inflated.

So the pressure generated there, whether you put it in submuscular or subglandular, is really determined by what location you're putting and, regardless whatever the pressure is, we always test for the worst case condition. We always test for the extreme conditions. So, therefore, we believe that even if it is within the range, it will maintain the properties.

DR. LI: Maybe one last -- I'll try to make it a last response.

If I were to take your data at completely face value, I think I would walk away with the impression that this device is near bulletproof. I mean you have to go in your testimony to rather extreme conditions to get rupture, fatigue. Nothing happens in the fold flaw.

Now, if I look at all of your tests, it actually looks extremely good, except for the --

MR. PURKAIT: It is good.

DR. LI: But you get 19 percent failure rate, and over 40 percent of them are revised.

MR. PURKAIT: But over 40 percent of those --

DR. LI: Which is an enormously high number.

MR. PURKAIT: If you break it down into cosmetic versus non-cosmetic --

DR. LI: Okay. So 20 percent. Take half.

MR. PURKAIT: Okay.

DR. LI: It's still a high number in three years. So that's the disconnect that I'm going after, right?

I mean your data looks excellent, right? I mean if I just looked at your data in and of itself, I would say from a materials and design standpoint it looks excellent. Okay? In the absence of any clinical data, you know, I'd probably have a completely different view, right? But the problem is I do have a clinical --

CHAIRMAN WHALEN: Just to focus upon this for a moment --

DR. LI: Yeah.

CHAIRMAN WHALEN: -- in the interest of

the flow of things, I don't think we're talking about mechanical testing per se anymore. We are talking about a highly clinically significant issue.

DR. LI: Well, I think they have to be linked to be meaningful.

CHAIRMAN WHALEN: Indeed, and we're going to proceed to other clinical issues. I guess refocusing, is there something specific that you would like to inquire about in terms of other mechanical testing that could have or should have been done?

DR. LI: Well, I guess, for instance, why haven't you looked at the effect of percent fill on the results as an example?

MR. PURKAIT: How do you mean?

DR. LI: In other words, doing a fold -- pick a test. Pick a dynamic test, fatigue, fold, whatever.

MR. PURKAIT: Let's say you mention about --

DR. LI: And then do an under fill -- do a 20 percent under filled, 20 percent over filled, and then --

MR. PURKAIT: Well, we don't suggest anybody to under fill. In our label copy, we clearly say, please, please, please don't.

DR. LI: So are you going to say that never happens?

MR. PURKAIT: I don't know, but we say that's what is supposed not to happen. We can't control this. We test in the nominal volume. That's the way they come in there.

You mentioned something. Just to clarify, the 2600 model, 2400 model, they were failed about 3,332 cycles, 16,118, those failures if you're looking back in the data was intentionally done to understand at what pressure and at what load that we can make a failure so that we can make a model. Those does not show a premature failure of those materials or those devices.

DR. LI: That wasn't clear in the application then in that case.

DR. CUNNINGHAM: If I could address your under fill issue from a clinical point of view, there is a body of information within plastic surgery

medical literature which I think would have almost all plastic surgeons feel very strongly that they should not under fill these devices because of the predilection for possible folds, fold flaws.

So I think most plastic surgeons know that there is a small range of fill which these devices are meant to perform within, and in fact, the way you determine what size implant you want to use is fairly precise because there are sizers which are connected with a tube and have the same footprint and dimensions as the implant which you place in, fill with saline until you reach the look or appearance that you think is appropriate for that patient and conforms with the discussions that you've had with that patient, and that gives you the amount of saline and allows you to choose which device to use.

So that surgeons are able to choose within that narrow fill range exactly which device is appropriate for the patient. So I think in clinical practice the real world is in this case perhaps more precise than the kind of range of testing that you might think we would have to do.

DR. LI: Well, in their own literature, in their PMA document, they said that -- I don't remember the exact phrase -- but that 20 percent over fill would be something that they would consider as an upper end of what might happen clinically.

So at 20 percent over fill, why weren't things tested at 20 percent over fill if that's what they stated as an over fill potential level?

MR. PURKAIT: I'm not sure I recall that, but maybe you are referring to the SPECTRUM product where you can go for adjustment purposes as we allow in our particular product.

DR. LI: Right.

MR. PURKAIT: Yeah, that is okay for the SPECTRUM, not for the regular fixed volume one.

DR. LI: Well, the other medical -- again, I hate to harp upon other medical devices, but typically in these there's a zone where you want the surgeon to be or the physician to be in the implantation of this device, but for reasons either by skill or by necessity, the person's anatomy or something beyond the physician's control, they can't

always hit that exact target, and they might have to do something, make a decision to go out of that extreme.

It happens. Right? It happens. You know you don't want it to happen. Most of the time it doesn't happen, but it happens. Right?

And you're faced with a case here where you have a very high number of failures and an alarmingly little analysis of those retrieved devices, right? And with the absence of that information of how the device actually deflates, I don't really know how you can discount any possible mechanism.

CHAIRMAN WHALEN: Any other questions, Dr. Li?

DR. LI: I think I'm done.

DR. ALLEN: Will I have an opportunity to respond?

CHAIRMAN WHALEN: Actually at the summation period if you wish, yes, but no.

And I'll get to your question in a moment. We're going to do the lead reviewers first and then we're going to go to general questions from the panel,

but we're going to -- okay. Dr. Burkhardt is here for the clinical study.

DR. BURKHARDT: That was all just on question one?

CHAIRMAN WHALEN: Actually we've not done question one yet.

(Laughter.)

DR. BURKHARDT: How do you want me to do this? Do you want me just to address question one?

CHAIRMAN WHALEN: No, no, no. This is just a general clinical study review, not with reference to any of the particular seven questions.

DR. BURKHARDT: Oh.

CHAIRMAN WHALEN: An overview.

DR. BURKHARDT: Okay. My thoughts on the clinical trial are, first, that -- my thoughts on this whole thing, I think is what you're driving at.

CHAIRMAN WHALEN: Yes, sir.

DR. BURKHARDT: The question of systemic illness and second generation problems, the reports are experiential. We don't have any scientific data on that, and what we have doesn't support it, and I

think they have to be disregarded.

What we have to worry about is local complications, and I'm not enough of an engineer to understand what happened, why this incidence was as high as it was, but my understanding is that if you eliminate needle punctures, which are there, and valve failures, that the major problem here is fold flaw failure, and my understanding of that -- you correct me if I'm incorrect -- is that that occurs because of abrasion, internal abrasion at the end of a fold.

In other words, it's not material fatigue. Am I correct about that? Because that's what I've been told.

MR. PURKAIT: To some extent fold flaw, that what we know of, we can speak for, could occur, could fail in at least three or four different ways. One of the mechanisms may be abrasion. The other would be, as I mentioned, a localized stress concentration. It's a creep factor.

If you have a two fold (phonetic) and some weight has been there for a long time, the material crimps, and that might give a pinhole, and it will

fail.

And the other probably would be a multiple fold that causes abrasion with different surfaces, and that might be a problem there.

DR. BURKHARDT: Thank you.

But the underlying problem is that they're going to fold. If you take an oval, three dimensional or round three dimensional thing with an oval cross-section and you stand it on its end, which is what we see in these patients when they stand up, for instance, they're going to get folds in them. The material is not perfectly elastic, and there's no way that I know of that you can get around that.

DR. LI: But, Dr. Burkhardt, perhaps to clear it up, there's some pictures that were difficult to see in black and white, but the FDA gave me the color versions. These are ten retrieved devices that Mentor supplied a photograph. They did a very nice job on these particular set of ten.

But if you look through these photographs of ten, the cracks which may have been the leak are delineated in black, and on Figure 6 there, you

actually see running across the horizon a white line that's a fold flaw, and you notice the two cracks that probably caused the leak are nowhere near it.

And if you look at the ten all the way through, more often than not the cracks and the pin holes that they identified were nowhere near the fold.

Now, in two cases, I think they were, but in the other eight they were not. So my point is this generation of these small cracks is not mimicked in any of their testing that I've seen.

DR. BURKHARDT: Well, these are implants that are removed, right? And --

DR. LI: For leakage.

DR. BURKHARDT: Yeah, for leakage, and what you're saying is that there's no permanent fold there that you can see now.

DR. LI: Well, on Figure 6 there's kind of a ghostly white line that runs across the horizon. I think it's Figure 6, the page I handed you. Now, some of them you'll see like a white line that goes across a gray background. That white line is the permanent fold, and the black lines that they've delineated are

where the cracks and pin holes are, and you'll see that oftentimes, most times that white line -- and sometimes it runs in all different directions -- is nowhere near the black lines that they identify as the source of the crack or the leak.

So in other words, this fold flaw thing still, after 30 years, may or may not be the reason these things leak based on the data that they've supplied.

DR. BURKHARDT: Well, I see some big black lines on here, but these were not cracks in the implant. Am I correct?

DR. LI: Yes. Yes, the short ones are all --

DR. BURKHARDT: Well, now let's find out about that before we decide that.

DR. CUNNINGHAM: I'm not sure exactly what picture --

DR. BURKHARDT: You've got big, long black lines in these pictures. Were those the cracks?

DR. LI: The long ones are wear. The short ones are cracks. If you see a really long black

line -- and correct me if I'm wrong -- but if I know your nomenclature, there is some implants that have very long black lines in them. Those are wear lines.

Other ones are very short black lines. The short black lines are cracks and holes.

DR. BURKHARDT: Okay, and so I guess I don't understand the point.

DR. LI: Well, the point is it is not so simple as you would like to make it, that if there's a fold it's bad, and if there's no fold, it's good, right? Because some of those have fold --

DR. BURKHARDT: Why not?

DR. LI: Because you've got the data right there. If folds and leaks were directly associated, the black line, the small black marks to indicate holes should be right on all of those ghostly white lines that are folds, and they are not.

DR. BURKHARDT: I think I'm not sophisticated enough to follow that line of reasoning. If the black lines are wear lines, which I would interpret as being the convex lines of the wear --

DR. LI: So, for instance, we're looking

at Figure 6 in your report. This line here, this off white, that's a fold line as I understand it, and these two lines are where the cracks are.

If the fold line was a source of cracks, these crack lines should be right on that line, and they are not.

DR. BURKHARDT: The black lines are described as wear lines, not cracks.

DR. LI: "Location of cracks in relation to the wear lines." Right. There's cracks and wear lines, right.

DR. BURKHARDT: There's a red line for a crack and black lines for the wear lines.

DR. LI: The problem is on this one unless --

CHAIRMAN WHALEN: In the microphone, please.

DR. LI: I guess the problem on this one is unless Mentor can say that the wear lines are not leak lines, I assume that when you had a wear line it may or may not be the source of a leak; is that correct?

So some of those wear lines may leak and some of those wear lines may not; is that correct?

MR. PURKAIT: That's correct.

DR. LI: Okay.

MR. PURKAIT: But I'm not sure which picture and what you are talking there because it's hard for me to really --

DR. LI: I understand. I'm just trying to fill in for Dr. Burkhardt how I was looking at those photos.

DR. BURKHARDT: Okay. Where were we? Nobody under fills these implants with any knowledge. You can't really legislate physician behavior, but --

DR. LI: But you could design for it.

DR. BURKHARDT: Well, maybe you can design for it, and again, I don't know. Maybe these could be improved, and that's your jurisdiction more than mine.

The leakage rate that is generally reported from fold flaw failure is in the five to ten percent range, and I don't remember the slides that you showed that brought it up to 19 or why it got to be so high.

Questions were raised about the texture to implant. I think it would be worthwhile for everybody to know why these implants were textured and what gave rise to the origin of the textured implant because it didn't have anything to do with easy insertion through a small incision.

A number of years ago a polyurethane covered implant came out from another company that was called the MIM (phonetic). It was widely accepted in plastic surgery and short term had a very small incidence of hardness or capsular contracture. Long term there's some question about what happened. Most of us think they all got hard.

At that time the companies that were producing the silicone implants, the silicone shell implants could not use a polyurethane covered implant because it was patented. So they had to try to do something to compete economically with the success of the polyurethane covered implant, and the response was to texturize the surface of the silicone implant.

Most of us who are in the field thought that that wouldn't accomplish anything at all, but